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### **DETAILED ACTION**

1. The examiner acknowledges receipt of IDS, request for continued examination under 37 CFR 1/114, request for extension of time, amendment and remarks, all filed 5/28/09. Claims 11 and 17 are amended. Claim 13 is canceled. Claims 11, 12 and 14-20 are pending.

### ***Response to Arguments***

2. Previous rejections that are not reiterated herein are withdrawn in view of the lack of sorbitan fatty acid esters, such as Sorbitan Monolaurate or Sorbitan Monopalmitate or Sorbitan Monostearate or Sorbitan Tristearate or Sorbitan Monooleate or Sorbitan Sesquioleate or Sorbitan Trioleate, in the cited prior art. Therefore, applicant's arguments with respect to the previous rejection that the Posanski reference does not teach sorbitan fatty acid ester is moot in view of the reference teaching sorbitan fatty acid ester with cyclosporine.

### ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 11, 12 and 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calne (US 5,212,155) and Posanski (GB 2 228 198 A) and Komiya et al. (US 5,504,068) in view of Armistead et al. (US 5,192,773) and Kao (US 5,262,423).

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5. Claim 11 has been amended changing comprising to consisting in the preamble.

However, claim 11 continues to recite further optional pharmaceutically acceptable excipients.

The excipients have not been limited and the broad recitation of excipients incorporated into the composition that was essentially closed opens up the composition include any excipient, and as such the composition is essentially open.

6. Please note that a claim which recites "consists of" the recited elements or steps cannot add an element or step. When the phrase "consists of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole. *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004) (The claims at issue "related to purified DNA molecules having promoter activity for the human involucrin gene (hINV)." *Id.*, 73

USPQ2d at 1365. In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from ... to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367. The court held that the claimed promoter sequence designated as SEQ ID NO:1 was obtained by sequencing the same prior art plasmid and was therefore anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. *Id.* at 1256 and 1259, 73 USPQ2d at 1366 and 1369. The court affirmed the Board's interpretation that

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the transition phrase "consists" did not limit the claims to only the recited numbered nucleotide sequences of SEQ ID NO:1 and that "the transition language 'comprising' allowed the claims to cover the entire involucrin gene plus other portions of the plasmid, as long as the gene contained the specific portions of SEQ ID NO:1 recited by the claim[s]" Id. at 1256, 73 USPQ2d at 1366.

7. Calne discloses composition comprising rapamycin and pharmaceutically acceptable carriers including olive oil or alcohol or propylene glycol or surfactant such as cremophor for oral administration in the form of tablet, caplet or capsule (abstract; column 3, lines 63-66; column 4, lines 4-10) to inhibit transplant rejections (abstract; column 4, lines 32-34); Calne also discloses that rapamycin can be used in combination with cyclosporin and one or more chemotherapeutic agents (column 4, lines 18, 46-50). The olive oil meets the limitation of triglycerides of claim 11 a). The surfactant meets claim 11 c).

8. Posanski discloses pharmaceutical composition that contains cyclosporine; carrier composition that contains oils, tenside having HLB of at least 10, triglycerides, natural oils and glycerol monooleate (abstract; page 7, third full paragraph; page 11, item A). Specifically, the components iii)-v), b and c of the composition of Posanski (page 7, 3rd full paragraph; page 11, under item A; page 18, under item B) are glycerides such as triglycerides (linoleic acid) and IMWITOR (pages 19-24) which have in the case of the fatty acid 6-22 carbons and have HLB of less than 10 in the case of the IMWITOR. An example of tenside having at least HLB of 10 is Miglyol 812 and Myrj 52 (see page 13, d.3; page 14, d.7; page 20, 1st full paragraph; examples 1 and 2).

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9. Rapamycin and cyclosporin are known immunosuppressive agents that have been described to inhibit transplant rejections according to Kao at column 1, lines 41-49 and Armistead at column 12, lines 25 and 26.

10. The olive oil of Calne and the sesame oil of Posanski meet the limitation of claims 11 b), 16 and 17 b). The dosage form of capsule of Calne encompasses the dosage of claim 20 and capsules are known to be either soft or hard and Posanski contemplates formulation of soft or hard gelatin capsules (see example 2).

11. Posanski describes the carrier composition of claims 11, 14-17. For Calne, the rapamycin is administered in mg/kg/day (see for example claim 2) as the effective amount. For Posanski, the cyclosporine is present at varying amounts of 5-10% (page 8, 2<sup>nd</sup> full paragraph), 15-25% (page 9, 2<sup>nd</sup> full paragraph) or 2-20% (page 12, 3<sup>rd</sup> full paragraph). Thus, one having ordinary skill in the art would use either the mg/kg/day or the % amount which is encompassed in the recited amount of claim 12 that would be effective to provide inhibition of organs after transplantation. Since the therapeutic agent rapamycin is the same as claimed, the solubility parameters of less 500 mg/1000 or sparingly soluble as recited in claims 11, 12 and 17 are met. Items (b) or (c) of Posanski is at 25-50% meeting the a) of claims 11 and the (b) or (c) of Posanski meets the fatty acid requirement of claims 14, 15 and 19. The tenside having at least HLB of 10 meeting claim 11 c) 17 c) is about 33% in example 2 so that the % amount in claims 11 and 17 recited is obvious over the disclosed amount. When the tenside is Myrj 52, which has 40 ethylene oxide units, the requirement that the surfactant under c) has 15-60 ethylene oxide units as recited in claim 18 is met. Also, for claim 17, the sorbitan skeleton being esterified with 1-3 acid radicals of saturated or unsaturated carboxylic acids having even number of 8-20

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carboxylic atoms is the process of forming the sorbitan. However, since Posanski teaches specific sorbitan, such as the palmitate, stearate, etc (see page 13, d.2), it flows that the sorbitan of Posanski would have the number of saturated or unsaturated carboxylic atoms recited in claim 17.

12. Komiya describes composition comprising cyclosporin and propylene glycol monocaprylate, isopropyl myristate, grams of PEG monostearate (25E0), polyethylene glycol, isotridecyl myristate, cetanol, olive oil, whale wax, sorbitan monostearate, polyoxyethylene glyceryl monostearate (5), stearic acid, diisopropanol amine, and diethyl sebacate and other excipients (see Examples 14-16).

13. Thus, Komiya teaches the carrier composition of claim 11 for cyclosporin, an immunosuppressant just as rapamycin, namely, the sorbitan monostearate is the sorbitan fatty acid ester of claim 11 ); isopropyl myristate, the olive oil, whale wax, and stearic acid are the oil components of claim 11 b); the PEG monostearate, polyoxyethylene glyceryl monostearate meet claim 11 c); and the propylene glycol monocaprylate, polyethylene glycol, isotridecyl myristate, cetanol, diisopropanol amine, and diethyl sebacate and other excipients meet the requirements for optional excipients of claim 11. Therefore, Komiya shows that the carrier composition of the claims has been used with cyclosporin except for the amounts in the range recited. Specifically, in Example 15, the oil component is greater than 12% (olive oil is at 12%); the PEG monostearate and polyoxyethylene glyceryl monostearate is at about 9%; the sorbitan is at about 2%.

14. The same is true for Posanski except that Posanski does not use sorbitan fatty acid ester. Both Komiya and Posanski formulate cyclosporin and not with rapamycin as active agent with

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the carrier composition of the claims. Calne discloses composition comprising rapamycin and/or cyclosporine and/or one or more chemotherapeutic agents, olive oil or cremophor agent and does not contain the sorbitan of claims 11 a) and 17 a). Rapamycin and cyclosporine are known immunosuppressant agents that are used to inhibit organ transplant rejection according to Kao at column 1, lines 41-49 and Armistead at column 12, lines 25 and 26.

15. Therefore, taking the combined teachings of Komiya, Posanski and Calne one having ordinary skill in the art at the time the invention was made and guided by the teaching in the art (Kao and Armistead) that rapamycin and cyclosporine are known immunosuppressive agents that have been described to inhibit transplant rejections, would have reasonable expectation that composition comprising rapamycin or cyclosporine, tenside having at least HLB of 10 and those having HLB of less than 10, oils, and sorbitan surfactants would effectively inhibit organ rejection after transplant since rapamycin and cyclosporin are poorly soluble and made soluble by the carrier composition.

16. Component b, the triglyceride in Posanski is at 25-50% (page 16, line 4) and meets the %limitation claim 11 b); d of Posanski, which meets the limitation of 11 c) is at 25-40% (page 14, 5 form the bottom) and meets percent amount of 11 c). Comparing the percent amounts of the various carrier components of Komiya and Posanski shows that the amounts of the components of the carrier composition can be varied to arrive at a concentration that would be expected to provide the desired immuno-suppression. Therefore, one having ordinary skill in the art at the time the invention was made would be motivated to optimize the composition to achieve the desired effect.

***Response to Arguments***

17. Applicant's arguments filed 1/19/20 as the arguments apply to the current rejections have been fully considered but they are not persuasive.

18. Applicant argues that Posanski does not teach sorbitan fatty acid ester of the claims.

19. The examiner agrees that Posanski does not teach sorbitan fatty acid ester of the claims and the rejection has been redone using a reference that teaches the combination of cyclosporin immuno-suppressant with sorbitan fatty acid ester.

20. Armistead and Kao are relied upon as evidentiary reference that Rapamycin and cyclosporin are known immunosuppressive agents that have been described to inhibit transplant rejections. Armistead and Kao were not relied to provide sorbitan fatty acid ester to Calne or Posanski.

***Claim Rejections - 35 USC § 112***

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 12, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Claim 12 depends on claim 11 and uses the language of comprising thereby adding other elements and making the claim indefinite.

24. A claim which depends from a claim which "consists of" the recited elements or steps cannot add an element or step. When the phrase "consists of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that

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clause; other elements are not excluded from the claim as a whole. *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004).

25. Review of Examiner Interview: In the interview of 4/21/2010, it was agreed to change "comprising" in all the other claims reciting that language to consisting in order to move the claims to allowance. It was also agreed to append the further optional language of claim 11 to claim 17. However, as was previously noted, the addition of optional excipient, which is any agent that qualifies as an excipient, opens up the claims so that composition comprising immuno-suppressant agent such as rapamycin, a), b) and c) and other excipients would meet the claims.

26. It is also brought to applicant's attention that the issue of the optional excipients was discussed in the interview of 23 Dec. 2009 when applicant appeared to agree to remove the presence of the optional excipients.

27. The presence of the requirement for the broad presence of excipients continues to keep the composition open even though the transitional language has been changed to consisting.

28. No claim is allowed.

29. In order to advance prosecution, applicant may consider calling the examiner to discuss the remaining issues.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on Monday to Thursday from 7 a.m. to 5:30 p.m.



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31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/  
Primary Examiner, Art Unit 1618